

REMARKS

I. Explanation of Amendments

Pursuant to the Patent Office's adoption of a revision to 37 C.F.R. § 1.121 (Manner of Making Amendments), applicants have voluntarily submitted amendments in the revised format as set forth above.

Claims 10 and 50 have been amended. In response to the Restriction Requirement dated September 3, 2002, Paper No. 8, Applicants elected Group I, corresponding to Claims 1-8, 10, 11, 47-51, 61, and 65 with traverse (Paper No. 9). The requirement has now been made final, and Applicants thus have cancelled Claims 9, 12-46, 52-60, 62-64 and 66-99 directed to the non-elected subject matter. These amendments are made in compliance with the restriction requirement and not for any reasons related to patentability. Applicants reserve the right to pursue claims to the non-elected subject matter in divisional applications. Claims 1-8, 10, 11, 47-51, 61, and 65 are currently pending.

As requested by the Examiner, the title has been amended to more accurately reflect the currently-pending subject matter.

As also requested by the Examiner, the material relating to $\alpha 2$ that was incorporated by reference in the application has now been formally added to the application in the form of new Figure 5 and Figure 6, and corresponding additions to the specification.

No new matter has been added by way of these amendments.

II. Formal Matters

Claims 50 and 51 are objected to as depending from non-elected claims. Specifically, Claim 50 depended from non-elected Claims 13, 14, or 15. In response thereto, Applicants have amended Claim 50 to recite a fusion polypeptide comprising a polypeptide encoded by at least one nucleic acid molecule of pending Claims 1, 2, or 3 fused to a heterologous amino acid sequence. This amendment is not a narrowing amendment, and was not made in view of any prior art. No new matter has been added by way of this amendment.

The Office Action states that incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication, is improper. The Office Action

requests that Applicants amend the disclosure to include the material incorporated by reference, accompanied by an affidavit or declaration stating that the amendatory material consists of the same material incorporated by reference in the referencing application. Specifically, the Office Action refers to the $\alpha 2$ subunit described in WO 99/41377 to Sheppard *et al.* Applicants note additionally that $\alpha 2$ is also referenced in Paszty *et al.*, WO 00/78964 in this section of the application.

In response thereto, Applicants have amended the application to include the nucleic acid and amino acid sequences for $\alpha 2$. For completeness, Applicants have included 2 mature forms of the molecule in the application. This amendment was not made in view of any prior art, and no new matter has been added by way of this addition. Applicants have included a declaration of Chris Paszty, Ph.D., which states, *inter alia*, that the amendatory material consists of the same material incorporated by reference in the referencing application. Please replace the previously filed sequence listing with the attached substitute sequence listing.

The title was deemed not descriptive. In response thereto, the title has been amended to more closely reflect the elected subject matter in the application.

III. Double Patenting Rejection

Claim 1 was provisionally rejected under 35 U.S.C. § 101 in view of Claim 1 of Applicant's copending Application Serial No. 09/723,970. This is a provisional double-patenting rejection because the 'conflicting' claims have not been patented.

Claims 2-8, 10, 11, 47-51, 61, and 65 have been provisionally rejected under obviousness-type double patenting as allegedly being unpatentable over Claims 1-8, 10, 11, 46-50, 61-67, 111, and 112 of Applicant's copending Application Serial No. 09/723,970.

Applicants disagree with these double patenting rejections, but note that they would be willing to file a properly executed terminal disclaimer in this application should any conflicting claims in Applicant's copending Application Serial No. 09/723,970 issue.

IV. The Objections and Rejections Under 35 U.S.C. § 101 and § 112 Should be Withdrawn

Claims 1-8, 10, 11, 47-51, 61, and 65 are rejected under 35 U.S.C. § 101, as allegedly not supported by either (i) a specific, substantial, and credible asserted utility, or (ii) a well established utility. The Office Action asserts that the polynucleotides of the claims encode a protein which has undetermined function or biological significance.

The PTO *prima facie* bears the burden of substantiating an assertion that a claim lacks utility. *In re Brana*, 51 F.3d, 1560, 34 USPQ2d 1437 (1995). Only if the PTO provides evidence showing that one skilled in the art would reasonably doubt the asserted utility, does the burden shift then to an Applicant to provide rebuttal evidence thereto. *Id.*

While lack of utility might exist where the described use involves an inherently unbelievable undertaking or where it involves implausible scientific principles, *Id.*, this is clearly not the case in the present application.

As early as 1994, there were five known glycoprotein hormone polypeptides which were placed into what is known as the “cystine-knot” growth factor structural superfamily, based on the crystal structure of human CG. Laphorn *et al.*, *Nature*, vol. 369, pp. 455-61 (1994). This superfamily includes the TGF-B (transforming growth factor beta), NGF (nerve growth factor) and PDGF (platelet-derived growth factor) gene families. The cystine-knot is formed by three intramolecular disulfide bonds, has a very distinct characteristic structure, and is responsible for the overall three-dimensional structure of all of members of the superfamily. *See Isaacs, Current Opinion in Structural Biology*, vol. 5, pp. 391-395 (1995). Figure 3 of the present application shows the three disulfide bonds (C12-C60, C36-C91, C40-C93, top lines) that would form the cystine-knot structure in $\beta 10$.

Those skilled in the art recognize these structural features that identify a sequence as a cystine-knot peptide. For example, the Figures in Applicants’ application compares the sequence and cystine-knot structures of $\beta 10$ with several known heterodimeric members of the glycoprotein hormone family (LH, FSH, TSH and CG). $\beta 10$ and the $\alpha 2/\beta 10$ heterodimer are polypeptides in this same family.

Applicants’ transgenic data demonstrate that mice overexpressing both the $\alpha 2$ and $\beta 10$ subunits showed bilateral thyroid enlargement with multiple follicular papillary adenomas and a resultant hyperthyroidism. Thus, in individuals producing an undesired excess of $\alpha 2$, and/or $\beta 10$

and/or the $\alpha 2/\beta 10$ heterodimer, the utility is specific (thyroid enlargement, multiple follicular papillary adenoma, hyperthyroidism), substantial (these are not insignificant conditions), and credible (one skilled in the art would not have any reason to question the utility in view of the level of skill in the art combined with Applicants' teachings). For example, where a patient demonstrates undesired levels of $\alpha 2$, and/or $\beta 10$, and/or the $\alpha 2/\beta 10$ heterodimer, and the accompanying symptoms of, e.g., thyroid enlargement, multiple follicular papillary adenoma, and/or hyperthyroidism, one skilled in the art would know to administer an antagonist (e.g., a selective binding agent) to $\alpha 2$, and/or $\beta 10$, and/or the $\alpha 2/\beta 10$ heterodimer to treat these conditions. Similarly, in the reverse situation, where a patient exhibits lower-than-desired levels of $\alpha 2$, and/or $\beta 10$, and/or the $\alpha 2/\beta 10$ heterodimer, one skilled in the art would recognize that it would be efficacious to administer one or both of these molecules (for example as the heterodimer) to the patient.

Why cause them?

Not known to exist - minute to exp.

TSH, for example, influences basal metabolism by regulating the production of thyroid hormones and is used clinically for enhancing the detection and treatment of thyroid carcinoma; see McEvoy, G.(ed.), *AHFS Drug Information*, pp. 2041-2042, American Soc. of Health-System Pharmacists, Inc., Bethesda, MD (1998). In addition, diagnostic tests for measuring TSH levels in the blood are commonly used in the art for determining the functional status of the thyroid gland when thyroid gland disorder is suspected. Human $\alpha 2/\beta 10$ would thus have similar clinical utilities as TSH, and is therefore useful for the treatment and diagnosis of thyroid gland-related diseases and disorders, as well as the additional therapeutic and diagnostic uses as described in the application. For example, human $\alpha 2/\beta 10$ selective binding agents (such as antibodies), would have similar clinical utilities to selective binding agents with specificity to TSH, and are therefore useful for the treatment and diagnosis of thyroid gland related diseases and disorders.

Not until a disease is found.

Withdrawal of this rejection is thus respectfully requested.

The Office Action also appears to allege that Applicants' data relating to the utility of $\alpha 2$ and $\beta 10$ as a heterodimer cannot apply to the utility of the $\beta 10$ subunit by itself. Applicants disagree. As demonstrated in the application (and explained herein), Applicants have set forth compelling evidence that the $\alpha 2/\beta 10$ heterodimer is a heterodimeric glycoprotein hormone that exists naturally *in vivo*, and that the $\alpha 2$ subunit naturally combines with $\beta 10$ *in vivo*. Thus, it is clear that utility associated with the $\alpha 2/\beta 10$ heterodimer can also be attributed to $\beta 10$, as a necessary component of the $\alpha 2/\beta 10$ heterodimer. The activity of the $\alpha 2/\beta 10$ heterodimer is thus dependent upon the presence and activity of $\beta 10$. Withdrawal of this rejection is thus respectfully requested.

Claims 1-8, 10, 11, 47-51, 61 and 65 are rejected under 35 U.S.C. § 112, first paragraph. The claims are said to cover allelic variants, splice variants, orthologs, or naturally occurring variants. The Office Action alleges that there is no written description of such variants, citing *Vas-Cath v. Mahurkar*, *Fiers v. Revel*, and *Amgen v. Chugai*, and *Fiddes v. Baird* (citations omitted). The Office Action in essence concludes that without actual sequence information for these variants, such a claim cannot stand. This rejection is traversed.

Applicants are not describing some broad, undefined class of compounds. It is important to bear in mind that the present nucleic acid molecules encode novel glycoprotein hormone polypeptides which are members of the cystine-knot growth factor structural superfamily. The cystine-knot is formed by three intramolecular disulfide bonds, has a very distinct characteristic structure, and is responsible for the overall three-dimensional structure of all of members of the superfamily. *w/ distinct functions*

One skilled in the art can readily determine these variants by first ensuring that the molecule possessed the requisite cystine-knot structure (formed by the three intra-molecular disulfide bonds described above). Figure 3 of the present application clearly shows the three disulfide bonds (C12-C60, C36-C91, C40-C93, *top lines*) that form the cystine-knot structure in $\beta 10$. Moreover, Figure 4 of the application shows an overlap of human $\beta 10$ and murine $\beta 10$ ortholog amino acid sequences, with percent identity and identification of their common amino acids. The percent identity between human and murine $\beta 10$ at the amino acid level is very high (greater than 93%).

The figures also show sequence overlap with other known family members. For example, Figure 2A shows an overlap of human TSH- β and human $\beta 10$, with percent identity and identification of their common amino acids. Figure 2B shows an overlap of human FSH- β and human $\beta 10$, and Figure 2C shows an overlap of human LH- β and human $\beta 10$, with percent identity and identification of their common amino acids. Figure 2D shows an overlap of human CG- β and human $\beta 10$ with percent identity and identification of their common amino acids.

Additionally, Applicants' relevant claims require that the encoded allelic or splice variant when heterodimerized to human $\alpha 2$ polypeptide, has an activity of the human $\alpha 2/\beta 10$ heterodimer. *Not fully described*

Thus, one skilled in the art could readily determine suitable variants which possess the requisite cystine-knot structures, and which when heterodimerized to human $\alpha 2$ polypeptide, have an activity of the human $\alpha 2/\beta 10$ heterodimer. One skilled in the art can readily determine whether this activity exists, using the transgenic teachings in Applicants' application. The suitable sequences to *What was Brian's comment on this.*

these molecules can be readily determined using the various overlapping sequences provided by Applicants, using knowledge common in the art. To limit Applicants' claims to exclude variants would be to unreasonably restrict the scope of Applicants' invention, and to invite infringement by third parties. Withdrawal of this rejection is respectfully requested.

Claims 1-8, 10, 11, 47-51, 61, and 65 are also rejected under 35 U.S.C. § 112, second paragraph. All Claims which recite "moderately" or "highly" stringent conditions are said to be indefinite. Applicants refer to pages 31-34 of the specification, and strongly disagree with the assertion in the Office Action that these sections are "vague". One skilled in the art would readily recognize the specific conditions set forth as providing more than suitable guidance to permit hybridization using known techniques. In fact, these sections cite art-recognized textbooks (such as Sambrook/Fritsch/Maniatis, and Anderson *et al.*), which would provide additional guidance should one skilled in the art require such supplemental information on hybridization techniques. Additionally, Applicants' have further limited the relevant claims such that when heterodimerized to human $\alpha 2$ polypeptide, the encoded polypeptides have an activity of the human $\alpha 2/\beta 10$ heterodimer. Withdrawal is respectfully requested.

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph. The nature of a "fragment of at least about 16 nucleotides" is said to be unclear. This is also said to apply to 'other' claims, such as Claim 3, part (f). Applicants note that rejections in an Office Action must should be stated with particularity. MPEP 707.07(d). The nature of this rejection is unclear, and no stated reasons are given as a basis for the rejection. Withdrawal is requested.

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to adequately point out that which Applicant sees as the invention. The Office Action states that there is no upper limit to the number of substitutions, insertions, deletions, or truncations specified in the claim.

In response thereto, it is noted that Applicants' invention is not *per se* a specific number of substitutions, insertions, deletions, or truncations in the claimed subject matter. Rather, the invention relates to nucleic acid molecules encoding beta-like glycoprotein hormone polypeptides and heterodimers thereof. The application provides ample disclosure to allow one skilled in the art to determine appropriate substitutions, insertions, deletions, or truncations to the claimed molecules. For example, Figure 4 shows an overlap of human $\beta 10$ and murine $\beta 10$ amino acid sequences, with percent identity and identification of their common amino acids. The percent identity between human and murine $\beta 10$ at the amino acid level is very high (greater than 93%). The figures also

show sequence overlap with other known family members (see Figure 2). Applicants submit that one skilled in the art, armed with this information, can readily determine which amino acid/s (and corresponding codons) can be substituted, inserted, deleted, etc. to achieve the desired activity of the molecule. It is submitted that to limit substitutions, insertions, deletions, or truncations to a specific number would be to unreasonably restrict the scope of Applicants' invention. No support is given by the Office Action for a numerical upper limit for such modifications, and withdrawal of this rejection is respectfully requested.

Claim 8 was rejected/objected to for its recitation of a "β10" polypeptide. Applicants disagree, and assert that the metes and bounds of the term can be readily discerned from the specification. For example, page 20, lines 30-32, and continuing onto page 21, lines 1-7 define β10 polypeptide as follows:

The term "β10 polypeptide" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, and related polypeptides. related polypeptides include: β10 polypeptide allelic variants, β10 polypeptide orthologs, β10 polypeptide splice variants, β10 polypeptide variants and β10 polypeptide derivatives. β10 polypeptides may be mature polypeptides, as defined herein, and may or may not have an amino terminal methionine residue, depending on the method by which they are prepared.

In view of this definition, one skilled in the art can readily determine the metes and bounds of the term "β10 polypeptide". Withdrawal of this rejection is requested. *Ad.*

Claim 10 was rejected/objected to in view of the term "native β10 polypeptide." In the interest of expediting prosecution, Applicants have amended Claim 10 to more clearly define the metes and bounds of the claimed subject matter. Specifically, Applicants have amended Claim 10 to state that the nucleic acid molecule comprises promoter DNA "other than the native promoter DNA for the β10 polypeptide" operatively linked to the DNA encoding the β10 polypeptide. Support for this amendment can be found in the specification at, e.g., page 58, lines 25-32. This amendment states the subject matter of the claim more succinctly without narrowing the scope of the claim, and was not made in response to any prior art. In view of this amendment, Withdrawal of the objection is respectfully requested. *sk.*

Claim 61 was rejected/objected to as being allegedly indefinite. The Office Action states that it is allegedly indefinite as to the metes and bounds of the term "human β10 polypeptide."

Applicants respectfully direct the Examiner's attention to, e.g., page 20, lines 30-32, and continuing *No.*

Expanded.

onto page 21, lines 1-7 defining $\beta 10$ polypeptides. In view of this definition, one skilled in the art can readily determine the metes and bounds of the term " $\beta 10$ polypeptide". Withdrawal is respectfully requested.

All claims are also said to be indefinite as to the metes and bounds of the term " $\alpha 2$ ". Although Applicants disagree with this rejected/objection, the current amendments and accompanying declaration obviate this objection. Withdrawal is requested.

Additionally, on page 6 the Office Action alleges that it is not predictable that $\alpha 2$ is the subunit with which the $\beta 10$ subunit naturally combines *in vivo*. In response thereto, Applicants point out that the specification demonstrated that mammalian cells readily secrete the $\alpha 2/\beta 10$ heterodimer after having been co-transfected with plasmids encoding $\alpha 2$ and $\beta 10$ (see pages 7-8 of the specification). A very robust phenotype was obtained in transgenic mice engineered to overexpress the $\alpha 2/\beta 10$ heterodimer (see page 9 of the Specification, lines 18-33, and page 10, lines 1-17). Thus, the *in vitro* heterodimerization in mammalian cells coupled with the *in vivo* biological activity of the $\alpha 2/\beta 10$ heterodimer (a strong phenotype in mice) are compelling evidence that the $\alpha 2/\beta 10$ heterodimer is a heterodimeric glycoprotein hormone that exists naturally *in vivo*, and therefore that the $\alpha 2$ subunit naturally combines *in vivo* with $\beta 10$.

V. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 1-5, 7, and 11 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Mahairas *et al.*, Locus AQ495547 (4/18/99).

The Office Action states that the nucleic acid in Mahairas would inherently hybridize to that of SEQ ID NO: 2, and also alleges that it would encode a polypeptide with at least one activity of the polypeptide encoded by SEQ ID NO: 2.

To invalidate a claim for anticipation under 35 U.S.C. § 102, a single reference must identify each and every feature recited in the claim sought to be invalidated. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991); *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Additionally, in order for a reference to be effective under 35 U.S.C. § 102, the reference must contain an enabling disclosure. See *In re Hoeksma*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968); MPEP 2121.1.

Applicants note that the genomic structure of the coding portion of $\beta 10$ has 2 exons separated by an intron. The Mahairas sequence is 405 base pairs, and contains part of this intron (23 bases; in

italics below), the whole of exon 2 (186 bases; in bold), the 3 base stop codon (TGA, underlined) and 193 bases of 3' flanking sequence.

1 TCTGTTTTTA TCTATGGGGA CAGAAACCCA TTCTGGAACC CCCCTATATT
 51 GAAGCCCATC ATCGAGTCTG TACCTACAAC GAGACCAAAC AGGTGACTGT
 101 CAAGCTGCCC AACTGTGCCC CGGGAGTCGA CCCCTTCTAC ACCTATCCCG
 151 TGGCCATCCG CTGTGACTGC GGAGCCTGCT CCACTGCCAC CACGGAGTGT
 201 GAGACCATCT GAGGCCGCTA GCTGCTCTCT GCAGACCCAC CTGTGTGAGC
 251 AGCACATGCA GTTATACTTC CTGGATGCAA GACTGTTTAA TTTCGACCAC
 301 ACCCATGGAG GAGGTTACCT GTCGCCCTT AGGTCCAGCT CAGGCAAAAG
 351 GCCCAAATGC AGCCTACTTA TGCTAAAAGT TCAAAACAAT ATTCGTGCCT
 401 TCACG

In total, Mahairas describes a BAC clone containing a piece of human genomic DNA. The sequence in Mahairas is completely unannotated, and importantly, identifies no introns, exons, genes or homologies to other molecules. No uses whatsoever are even remotely mentioned. Mahairas thus does not contain an enabling disclosure.

Additionally, cysteines C12, C36, and C40 are encoded by exon 1 and are not present in the portion of the truncated β 10 polypeptide encoded by the Mahairas sequence. Thus, not only does the Mahairas lack any description of the mature form of β 10 polypeptide, but it would not be able to adopt a cystine-knot configuration. The 3-D structure of the significantly truncated Mahairas β 10 polypeptide would be completely unlike that of mature β 10 polypeptide and thus the Mahairas β 10 polypeptide would be completely inactive with regards to heterodimerizing with α 2 polypeptide and binding to the α 2/ β 10 receptor(s).

The Office Action admits that it cannot be determined whether the molecule from Mahairas possesses the properties recited in the claims, and further acknowledges that it cannot be determined whether it is sufficient to heterodimerize with α 2. But adds that, "it is fairly certain that it would at least have the activity of β 10 of comprising at least one antibody-binding epitope of such." However, Applicants' note that claims do not recite the term "antibody-binding epitope." Withdrawal of this rejection is thus requested.

Can't exclude - it's an activity!

VI. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 6, 8, and 48-50 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over G.G. Mahairas, above, in view of Sibson *et al.*, WO 94/01548.

Sibson *et al.* is said to teach the use of a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such DNA's.

The PTO bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); *See also*, MPEP 2142. Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956.

Claim 6 relates to a eukaryotic host cell comprising a vector, wherein the vector comprises the nucleic acid molecules set forth in Claims 1, 2, or 3. Claim 8 describes a process of producing a β 10 polypeptide comprising culturing a host cell of under suitable conditions to express the polypeptide, and then optionally isolating the polypeptide from the culture.

Mahairas was discussed above. Sibson is directed to specific human nucleic acid fragments (SEQ ID NOS: 1 to 1193) isolated from adrenal or placental tissue, or from bone marrow.

Elements of separate patents (or publications) cannot be combined when there is no suggestion of such combination anywhere in those patents (or publications)... and a court (or the PTO) should avoid hindsight). *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593, (Fed. Cir. 1987), citing *ACS Hospital Systems*, 220 USPQ 929, 933 (Fed Cir 1984).

Additionally, to support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention, or the examiner must present a convincing line of reasoning as to why one skilled in the art would have found the claimed invention to be obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Intf. 1985); *See also* MPEP 2144-2144.09.

An analysis under 35 U.S.C. § 103 requires consideration of (i) whether the prior art would have suggested to one skilled in the art that they should make the claimed composition, and (ii) whether the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). However, both the suggestion and the reasonable expectation of success must be *founded in the prior art*, not in the applicant's own disclosure. *Id.*

There is absolutely no suggestion in the cited references to combine Mahairas and Sibson. Moreover, even if one skilled in the art were motivated to combine these references (and Applicants maintain they would not) the combination of Mahairas and Sibson in no way would suggest Applicants' invention. Mahairas provides incomplete, genomic DNA, with an intron, and absolutely

Sibson
genes
motivation

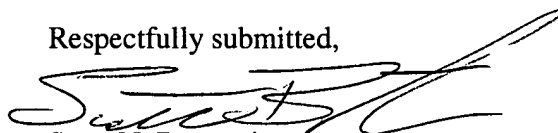
no reading frame, for an inactive portion of the β 10 molecule, which would not fold properly. Sibson relates to completely *unrelated* DNA sequences, and methods of producing the same. There is simply no suggestion whatsoever in the cited references of such combination. Furthermore, there is simply no indication in the cited art that would reveal a reasonable expectation of success in arriving at Applicants' invention as claimed in Claims 6, 8, and 48-50.

To reach a proper determination under 35 U.S.C. § 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. MPEP 2142. Knowledge of applicant's disclosure *must be put aside* in reaching this determination. *Id.* (emphasis added). Viewed without hindsight, one skilled in the art would simply not have been motivated to combine Mahairas and Sibson, let alone have *any* expectation whatsoever of success with being able to arrive at Applicants' invention. The claimed invention as a whole simply is not in any way suggested by the cited references. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the amendment and remarks made herein, the applicants believe that claims 1-8, 10, 11, 47-51, 61, and 65 are in condition for allowance, and respectfully request reconsideration.

Respectfully submitted,



Scott N. Bernstein
Attorney for Applicants
Registration No: 38,827
Phone: (805) 447-4128
Date: May 21, 2003

Please send all future correspondence to:

US Patent Operations/ SNB
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799